V. Short-Course Antiretrovirals in Antenatal Settings

Pharmacology, Safety, and Contraindications of AZT and Other Perinatal Prevention Drugs

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I will be addressing issues about the use of antiretrovirals in pregnancy and in infants in terms of toxicity, with a focus on ZDV followed by a few remarks about other antiretrovirals.

I will address three separate issues: What are the available data on the short-term safety of ZDV prophylaxis in women and infants? What are the data on the long-term safety of the drug in these groups? And what preclinical and clinical data are available on other antiretroviral drugs in terms of their potential use for perinatal transmission prophylaxis?

The first thing that I will discuss is the short-term safety of ZDV prophylaxis, and I will discuss three separate studies: results from the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076, data from the Bangkok study (which is discussed in much more detail by Dr. Shaffer), and some data from the Antiretroviral Pregnancy Registry.

In reviewing potential toxicities, it is important to remember differences between PACTG 076 and the Thailand short-course ZDV regimen. In PACTG 076, ZDV was begun between 14 and 34 weeks gestation and continued throughout pregnancy, avoiding first trimester exposure. The median duration of ZDV in the trial was 11 weeks. ZDV was given intravenously during labor, not to reduce maternal viral load, but to achieve virucidal levels of the drug in the fetus at the time of maximal viral exposure during passage through the birth canal. Finally, ZDV was given to the infant for 6 weeks.

In contrast, in the Thailand study ZDV was started at 36 weeks gestation. With a median duration of 24 days, the drug was given orally during labor, and no drug was given to the baby. So one might anticipate less ZDV toxicity to be observed with the short-course regimen.

First, I will discuss ZDV toxicity to the fetus. Fetal toxicity observed with drugs that are started early in pregnancy (e.g., < 4 weeks gestation) usually manifest by abortions or miscarriages. The toxicity manifestations for drugs started between 4 and 12 weeks are potential congenital abnormalities and, for drugs administered later, primarily intrauterine growth retardation.

What was observed in PACTG 076? Fetal toxicity was monitored by serial ultrasounds in the study; no patterns of abnormalities in amniotic fluid were seen and no abnormalities were seen in fetal growth or development. At birth, infants in the ZDV and

placebo groups were comparable in birth weight, length, and head circumference, as well as the incidence of prematurity. The incidence of minor and major congenital abnormalities were similar, without any specific pattern seen. This slide shows you the types of congenital abnormalities observed; there was no difference between the study arms. Minor abnormalities were seen in 13 percent of ZDV and 17 percent of placebo recipients; cardiac malformations, 2 and 4 percent, respectively; CNS malformations, 2 and 0.5 percent; and other malformations, 5 and 4 percent.

In the Bangkok short-course ZDV study, the groups also were comparable at birth in terms of birth weight, birth length, head circumference, and prematurity. Five percent of infants in each group were premature. Low birth weight was observed in 7 percent of the infants in the ZDV and 10 percent of the placebo group. Congenital malformations were seen in only 1 percent of the population, two cases in the ZDV, and two cases in the placebo group of infants.

The potential teratogenicity of in utero ZDV exposure is also being evaluated through the International Antiretroviral Pregnancy Registry, which is a voluntary confidential registry in which the health care provider provides information about antiretroviral use in pregnancy, without any name, and the Registry follows up for birth outcome. This is an international registry, and I would urge people to report information about antepartum ZDV use to this registry so that we can get a better idea about teratogenicity.

These are the last quarter's data on reported use of ZDV during pregnancy. The proportion of live births with birth defects were no different than that in the general population; birth defects were observed in 1 percent of women with first trimester exposure and 4 percent of women with exposure in all trimesters. In those infants who did have congenital abnormalities, no specific pattern of defects were seen. The denominator of reported cases, however, was only 281, and thus the ability to draw any definitive conclusions is limited.

What about fetal and infant deaths with ZDV use? These data are from the PACTG 076 study. There were 15 deaths during the trial: 8 in the ZDV, and 7 in the placebo group. Eight of these deaths occurred among fetuses and newborns: 5 in the ZDV, and 3 in the placebo group. There were 7 deaths after the neonatal period, primarily due to HIV infection, with 1 due to trauma.

This slide shows the causes of death among the fetuses and newborns in the ZDV group and the placebo group; there was no association with the treatment or any particular pattern in terms of causes of death.

In PACTG 076, 22 infants stopped treatment because of serious grade 3 or 4 toxicity–11 in each group. The only difference between the two groups was in the occurrence of anemia, which was defined as a hemoglobin count of less than 9. This occurred in 44 infants in the ZDV and 24 infants in the placebo group, which was a statistically significant difference.

However, the occurrence of serious grade 3 anemia (hemoglobin less than 7) occurred in only four infants: one in the ZDV, and three in the placebo group. So, while a mild anemia was seen, severe anemia really was not any different between the two groups. The incidence of all other side effects, including adverse pregnancy outcomes and neurologic diagnoses, were similar between the two groups.

This graph shows you infant short-term serious toxicity by type and by treatment. There are no significant differences between the two groups. Serious anemia (grade 3 to 4) was observed only in 1 percent of patients in the ZDV and 3 percent of patients in the placebo group. Neutropenia was observed in 17 percent of ZDV patients and 23 percent of placebo patients, and other hematologic toxicity occurred in 1 percent of each group. Serious chemistry toxicity was observed in 10 and 13 percent of ZDV and placebo groups.

This graph shows the mean hemoglobin level in the infants by treatment. Infants in the ZDV group had a somewhat lower hemoglobin at birth. The peak difference between groups was at 3 weeks of age, with the maximum difference in mean hemoglobin being 1 gram per deciliter. This persisted to about 6 weeks, but resolved on its own without requiring either transfusion or erythropoietin by 12 weeks of age.

These data are taken from the Bangkok trial summary on hematocrit by study arm, which Dr. Shaffer discusses in more detail. There was a minor, but statistically significant, difference in terms of hematocrit at birth in the ZDV versus placebo group infants. However, the majority of infants had no toxicity. Although the mean levels were different, there were no differences in terms of higher grade serious toxicity and there were no grade 4 toxicities in the Bangkok study.

Based on these data, we can conclude that in utero ZDV exposure appears to be well tolerated by the fetus and the infant, even with longer duration exposure. The only short-term toxicity observed was a transient, self-resolving anemia (primarily observed in PACTG 076 infants who had longer in utero exposure and received ZDV as newborns).

In terms of maternal toxicity, treatment was well tolerated in the PACTG 076 study; treatment was discontinued in only six patients, three in each group. Maternal toxicities were balanced between the two groups, and there were no significant differences between the ZDV and placebo recipients for either hematologic or chemistry toxicities.

Additionally, at 6 months postpartum there was no difference in CD4 lymphocyte count between the two groups; most women had CD4 counts that remained above 300 μL. Only four women had CD4 counts that dropped below 200 μL: one in the ZDV, and three in the placebo group. The number of women receiving open-label ZDV postpartum was 19 in the ZDV and 21 in the placebo groups.

These are data from the Bangkok summary. As observed in PACTG 076, there were no significant differences in terms of toxicity of any grade, and grade 4 toxicity was extremely unusual in either group.

We can conclude that there does not appear to be any major short-term maternal toxicity associated with either more prolonged or short-course antenatal ZDV use.

But what about long-term safety for the infants? We have two ways we are evaluating this: PACTG 219 is a protocol that follows infants born to mothers who have received antiretrovirals during pregnancy as part of a perinatal PACTG protocol; the study follows these infants through age 21 with periodic intensive evaluations. We also have a number of prospective cohort studies that can provide longer-term follow-up data.

In PACTG 219, neurologic, immunologic, chemistry, and multiple other types of toxicity are monitored. Preliminary results were reported by Culnane, et al., at the Infectious Disease Society of America meeting last year, involving 333 uninfected infants from PACTG 076. All of these infants were over age 15 months at the time of the report, and the median age of the infants in this report at the time of the last visit was 4.2 years, with some as old as 6 years.

This slide shows you age-related CD4 counts in these uninfected children with in utero exposure. In healthy, uninfected children, it is normal to see high CD4 counts at birth that gradually decline with age, and this is exactly the pattern you see in these children. There was no significant difference between the groups in CD4 count over time.

This slide looks at neurodevelopmental outcome. It shows results of the Bayley tests from age 24 months. The mental index and motor index were in the normal range, and there were no significant differences between children in the ZDV and placebo groups.

This slide shows you weight Z-score for the children. The zero would be a child growing normally along the 50th percentile; a negative value would mean growth at less than the 50th percentile; and a positive value would mean growth better than the 50th percentile. There was no significant difference between the two groups; if anything, children in the ZDV group have a little bit better growth than the placebo group.

What other concerns are there? ZDV is positive on in vitro and animal screening tests for carcinogenic potential, as are all of the nucleoside analogues. High-dose lifetime administration of ZDV to rodents was associated with the development of benign squamous cell vaginal tumors in about 13 percent of the female rodents. There is a difference in terms of metabolism of ZDV between rodents and humans. High levels of unmetabolized ZDV are excreted in the urine in rodents and can reflux back into the vagina in rodents, whereas in humans it is the glucuronide metabolite that is excreted in the urine. It was hypothesized that the vaginal tumors might be a topical effect of exposure of the vaginal rodent mucosa to high concentrations of ZDV. Scientists at Glaxo have been able to replicate these rodent tumors by application of high concentrations of ZDV to the vaginal mucosa of mice who have not had systemic exposure. Whether this is systemic or topical toxicity and only relevant to rodents is unknown.

Additionally, there are two transplacental studies in mouse models that have had different results. These are studies in which ZDV is given to the pregnant mouse and then the infants are followed up for potential cancer outcome. In one study from the National Cancer Institute, very high doses of ZDV were administered during the last trimester of gestation in mice. These doses were near the lethal fetal dose. An increased rate of tumors

of the lung, liver, and vagina in the adult pups was observed after 12 months of follow-up.

Another study from Glaxo used ZDV doses during pregnancy approximately three times the level achieved in humans (more consistent with the daily dosing in PACTG 076); ZDV was also given to the pups. In this study, no increase in unexpected tumors was observed; the same kind of vaginal tumors seen with lifetime exposure was observed, as these pups also had lifetime exposure.

The relevance of these animal data to humans is unknown. The NIH had a blue ribbon panel review these data in January of last year, and the panel concluded that the known benefit of ZDV in reducing perinatal transmission of HIV, a fatal disease, outweighed the hypothetical risk of carcinogenicity with ZDV; however, they also concluded that long-term follow-up of antiretroviral-exposed infants is important.

We have evaluated carcinogenic risk for at least the short term by combining data from the PACTG 076/219 children with another large prospective study, the Women and Infants Transmission Study in the United States. This evaluated 727 children who had in utero ZDV exposure, most for prolonged times (median of 11 weeks), who were followed for more than 1,100 patient-years. While reassuringly no tumors were observed in any of these children, including the infected children, clearly we need further follow-up to be able to provide more definitive data on carcinogenicity.

Long-term safety of the regimen in women is also being evaluated. I will talk a little bit about the resistance studies and PACTG 288, which is a 3-year follow-up study of women who participated in PACTG 076, after they have delivered.

Resistance was evaluated by Eastman, et al., (published in the *Journal of Infectious Diseases* this year) by codon 70 and 215 genotyping of plasma virus in all transmitters, 50 percent of nontransmitters in the ZDV arm, and all women who had prior ZDV at entry.

The high-level resistance (215 mutation) was not seen in any women at entry or delivery. The prevalence of codon 70 mutation at entry was low–3 percent (one woman). This was a woman in the placebo group who had no prior ZDV exposure and who entered the study with a mixture of codon 70 and wild type virus. She transmitted HIV to her infant.

The development of resistance while on the study drug was also low–3 percent (one woman). This woman (who was in the ZDV arm) had no resistance at entry and developed a mixed wild type/codon 70 virus at delivery; she did ***not*** transmit HIV to her infant. The development of the codon 70 mutation was not associated with transmission; the vast majority of infants who were infected were from mothers who did not have resistant virus.

This slide shows preliminary data from PACTG 288 that will be presented at the AIDS meeting in Geneva. Women enrolled in PACTG 076 could enroll in this study at 6 months postpartum. Forty-four percent of the women enrolled in PACTG 076 entered PACTG 288, including nearly 50 percent of those who were originally in the ZDV arm. The mean follow-up of women in this report is 2.4 years. More women in the placebo arm received antiretrovirals during the postpartum period–38 percent of woman receiving ZDV

compared with 52 percent receiving placebo. There was no significant difference in time to AIDS or death between the ZDV and placebo arms at 2.4 years. Forty-eight women had HIV disease progression, 27 in the ZDV and 21 in the placebo group (p value = 0.42). There was one death in each arm. Thus, long-term side effects at almost 2½ years postpartum also appear to be minimal for the woman.

I want to end by discussing what we know about other antiretroviral drugs. In terms of the nucleoside antiretrovirals, only ZDV and 3TC have known pharmacokinetics in pregnancy; we currently have ongoing studies on ddI and d4T. ZDV and 3TC both appear to be able to be given in normal adult doses in pregnant women.

All of the nucleoside analogues are positive on at least one in vitro carcinogenicity evaluation or on long-term animal studies. For example, ddC is associated with the development of thymic lymphomas in rats. All of these analogues also cross the placenta. 3TC and AZT cross the placenta with the most efficacy, while ddI crosses with less efficacy. Thus, like ZDV, all of these drugs have some potential for fetal toxicity. At present, ZDV is the drug that has known benefit for the fetus in terms of reducing perinatal HIV transmission.

In terms of the nonnucleosides, only Neverapine has been studied in pregnant HIV-infected women, and only with a dose given at labor and a dose to the newborn (in a study in the United States and another study in Uganda). The drug crosses the placenta and achieves nearly equal levels in the mother and infant at birth. The drug has a prolonged half-life in the neonate. These drugs appear to be less worrisome in terms of animal carcinogenicity studies, but many of the relevant studies have not been completed. Delaverdine is teratogenic in rodents at high doses. Although Neverapine is under study in Uganda and the United States for prevention of HIV transmission, results are not yet available.

In terms of the protease inhibitors, all four currently available protease inhibitors are being studied in the United States among pregnant women as triple therapy, but no data are available yet. There are conflicting data about the ability of these drugs to cross the placenta. In rodents, some of the drugs appear to cross the placenta relatively well, but this is not the case in rabbits. If the drugs do cross the placenta, because they are metabolized by the liver, there is the potential for fetal toxicity because of the immature liver metabolism in the neonate. The ability of protease inhibitors to reduce transmission is unknown.

I now will discuss drugs that may be used in the future. Abacavir is another nucleoside analogue; its major toxicity is a severe hypersensitivity reaction, which very rarely can be fatal. We do not have the preclinical studies on this drug, although we do have a study in development.

Adefovir (PMEA) is a nucleotide analogue reverse transcriptase inhibitor. In animal studies, use in pregnant rodents has been associated with pregnancy resorption, low birth weight, and neonatal deaths, as well as thymic depletion.

Another nucleotide analogue, bis-POC PMPA, has been shown in post-exposure

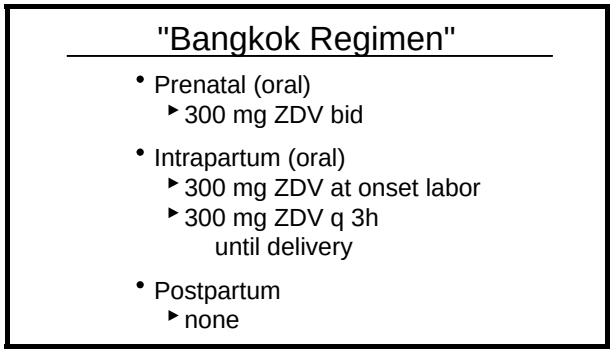
studies to prevent SIV transmission in a perinatal model, including when administered postpartum. A problem with this drug is that bony abnormalities, including deformities and fractures, have been seen in about 20 percent of infant monkeys born to mothers receiving high doses in the last trimester and continued in the infant. However, with very short-term use (such as a single dose), this may not be a problem. A study to look at a single dose of this drug in labor and to the newborn is under design.

Efavirenz is a new nonnucleoside reverse transcriptase inhibitor. Like Neverapine, the major toxicity is rash. The major caution on use of this drug in pregnancy is that there has been severe toxicity seen in monkey in utero animal studies, including anencephaly, microphthalmia, and cleft palate.

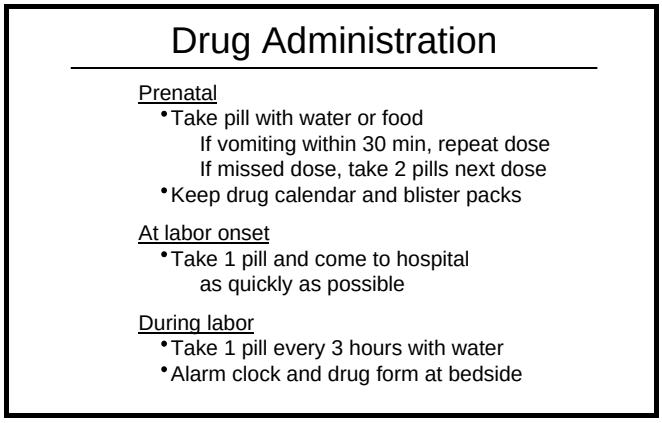
Amprenavir is a new protease inhibitor; the primary toxicity is again rash. We do not have any data in terms of preclinical studies, and at this time no protocol to study this drug in pregnant women is underway.

Dosage, Administration, and Monitoring in the Short-Course AZT Phase III Trial to Reduce Perinatal HIV Transmission, Bangkok, Thailand

Presented by Nathan Shaffer, M.D.
The HIV/AIDS Collaboration, Bangkok, and CDC



As a reminder, the short-course Bangkok regimen consisted of prenatal oral ZDV, 300 mg twice a day starting at 36 weeks, then intrapartum oral dosing of 300 mg of ZDV at the onset of labor at home and 300 mg of ZDV every 3 hours until delivery. There was no postpartum dose to either the mother or the infant. And, importantly, there was no breast-feeding.

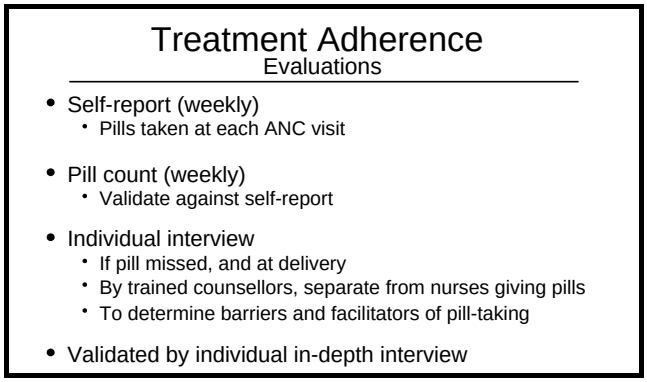


We provided practical instructions to the mothers about drug-taking. The women were instructed to take the antenatal pills with water or food. If a woman had any vomiting within 30 minutes of taking the pill, she was to repeat the dose. If she missed a dose at home and knew about it, she was to take two pills at the next dose, but not to double up more than that.

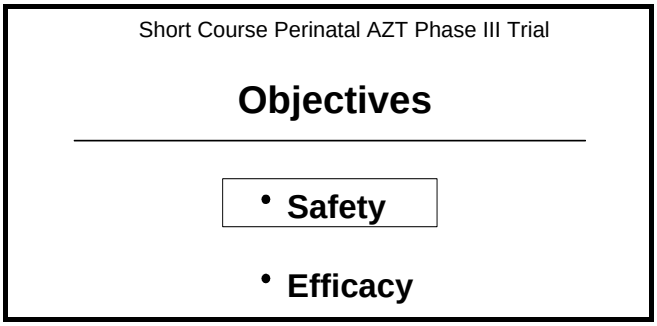
The women were asked to keep a drug calendar to record each time they took a pill. They were given a standard form for this, and the calendar form was reviewed weekly when the woman came to the antenatal clinic. The study drugs were given in blister packs. The morning and nighttime doses were marked on the blister pack, and the women were instructed to return each week with their used blister packs of pills.

The women were instructed to take one pill at the onset of labor and to come to the hospital as quickly as possible. You saw in a prior presentation that the average time for the women to get to the hospital was about 2 hours. During labor they were to take one pill every 3 hours with a very small amount of water, within the allowances for OB management.

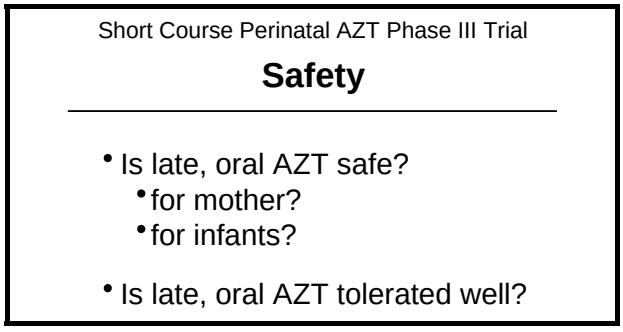
To help ensure every-3-hour labor dosing, we instituted a system that worked very well. At each bedside we had an alarm clock set for every 3 hours. The woman was actively responsible for the labor dose, just as she was for the antenatal dose. She had a schedule sheet by her bed. She set the clock with the nurse, and she knew when the alarm clock went off. In labor rooms, nurses can be busy with emergencies. So the woman was involved with the monitoring of her own labor dose. We think this is a practical step to facilitate or enhance labor dose compliance.



We evaluated the pills and the self-reports weekly when the woman came back to report on her study drug experience, to discuss side effects, and to get the new drug for the next week. We did a pill count and we validated the pill counts against the self-report. There also was an individual interview with each woman, usually by one of the social workers on our team who was separate from those actually handing out drugs and going over the drug. We wanted to have a separate interview to make the woman comfortable with talking about or reporting any possible problems that she was having with the drug. We also did some validation by individual in-depth interviews to make sure that the quantitative data that we were getting seemed to be reliable.



The next part of my talk is about our evaluation of safety. In my previous presentation, I discussed efficacy in the trial.



The safety questions that we had were: Is late, oral AZT safe? Is it safe for and well tolerated by the mother, and is it safe for and well tolerated by the infants? Lynne Mofenson has just reviewed what we know about all of this. The 076 trial did not detect serious safety problems, and we believed we likely would have fewer problems.

Safety and Tolerance

Active surveillance for toxicity and adverse events

Maternal monitoring during ANC visits, delivery and 1 month postpartum

- Weekly evaluation:
  - Clinical signs and symptoms
- Bi-weekly laboratory evaluation:
  - Hematologic, hepatic and renal toxicity
- Standard ACTG tables for toxicity (adults)

Infant monitoring

- Physical exam at each study visit
- Hematologic evaluation at birth and 2 months
- Morbidity from birth through 2 months

We did active surveillance for toxicity and adverse events. The mothers were monitored during each of their weekly ANC visits, at delivery, and at 1 month postpartum to look for clinical signs and symptoms; we also conducted biweekly laboratory evaluations. We used the standard ACTG tables for toxicity for adults to do a fairly rigorous monitoring for any problems.

The infants had physical examinations at each study visit, which initially were at birth, 1 month, 2 months, 4 months, and 6 months. Subsequently, infants had a hematologic evaluation at birth, 2 months, and 6 months. To monitor for immediate adverse events that might be associated with drug-taking, since there was no infant component, we concentrated on birth to 2 months, although we are following the infants through 18 months.

Mother Toxicity Monitoring (all grades, 1-4)

37 W ANC visit through 1 M postpartum

	AZT	Placebo
Respiratory	20	19
Neuromuscular	23	25
Cardiovascular	5	5
Gastrointestinal	43	37
Prgnancy problems	34	28
Laboratory abnormality		
Hematol/Chemistry	101	89
Urine test	64	67
Others	34	40

We did not find evidence of toxicities in the AZT arm compared with the placebo arm. This slide lists any type of toxicity, grade 1 through 4. Most of these are grade 1 or 2

and are essentially minor. And, as I mentioned, no women had to discontinue the drug or discontinued on her own because she felt she was experiencing toxicity or could not tolerate the drug.

Mother Serious Adverse Events
by treatment group, diagnosis

	AZT	Placebo
Anemia	13	10
Elevated liver enzymes	8	3
Pregnancy problem	1	1
Diarrhea	-	1
Total	22	15

This slide lists the serious adverse events, grade 3 or 4, that were reported as part of our monitoring process during the trial. Again you can see that there was no evidence of imbalance between the groups. Anemia was primarily detected right after delivery, so this was mostly associated with postpartum hemorrhage or bleeding, and there was not a significant increase between the AZT group and the placebo group.

We did have a small number of women in the AZT group with elevated liver enzymes, although this was not statistically significant. These abnormalities did resolve without any special treatment after the drugs were discontinued. We did not note any particular pregnancy problems associated with ZDV.

Child Serious Adverse Events
by treatment group and child HIV infection status

	AZT	Placebo
HIV-infected	5	9
HIV-uninfected	10	11
Unknown	1	1
Total	16	21

In terms of serious adverse events among the children, this slide compares the AZT and placebo groups and the HIV infection status of the children. At the bottom you see the totals of all serious adverse events among the children. There were 16 in the AZT group and

21 in the placebo group, so certainly there was no concern there. We had one neonatal death associated with cardiac anomalies which was in a child of unknown HIV infection status.

Child Serious Adverse Events
by treatment group, diagnosis

	AZT	Placebo
Infant hospitalizations	9	16
Congenital anomalies	4	3
Anemia	2	2
Neonatal deaths	1	-
Total	16	21

In terms of the child-specific adverse events that we did note, we considered any hospitalization for more than 1 week in the first 2 months of life to be one of our criteria for serious adverse events. Again, we did not see any increase in the AZT group.

We now have slightly more congenital anomalies than were reported in the preliminary study report, and I will show that on the next slide. Again, there was nothing that was particularly worrisome. The one neonatal death in the study was a child that died at 12 hours with pulmonary and cardiac abnormalities.

Congenital Anomalies

	AZT	Placebo
HIV-Infected	Congen. heart	Microcephaly Cleft palate
HIV-Uninfected	Pyloric stenosis Hydrocephalus Congen. heart	Pyloric stenosis

These are the congenital anomalies that were recognized and reported in the study, and there basically was no difference. There were four congenital anomalies reported in the AZT group and three that were recognized and reported in the placebo group. The two cardiac anomalies were both minor, and the children are doing fine. The hydrocephalus is stable and the child is being followed clinically at this point.

Mother Hemoglobin and Hematocrit

36 W GA and delivery - mean (range)

	AZT	Placebo
36 W GA		
Hb	11.7 (9.0-15.4)	11.8 (8.8-15.6)
Hct	35.1 (27.0-45.5)	35.4 (26.8-46.6)
Delivery		
Hb	10.8 (5.8-14.5)	11.1 (6.3-15.3)
Hct	31.9 (17.0-43.2)	33.0 (19.1-44.8)*

* $p < 0.05$

As Lynne Mofenson mentioned, we did find a small difference in the mean hemoglobin and hematocrit levels, but this was not clinically significant. This slide shows that, at 36 weeks (at entry before starting drug), the two groups of women–AZT and placebo recipients–were comparable. In mothers at delivery there was a statistically significant difference in the hematocrit and hemoglobin, with the AZT recipients having slightly lower hematocrits. But this was not clinically significant, and there was no imbalance in terms of grade 4 toxicities with this. Nevertheless, it is interesting that even with 24 days of therapy, there was a detectable difference overall.

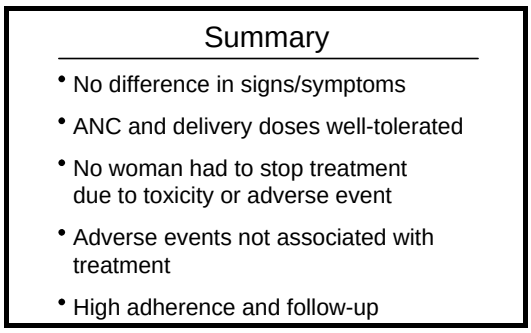
Child Hemoglobin and Hematocrit

birth and 2 months of age - mean (range)

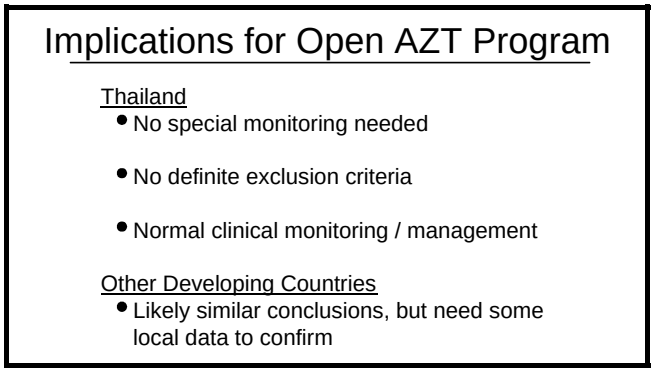
	AZT	Placebo
Birth		
Hb	15.0 (10.3-19.1)	15.9 (11.7-21.3)*
Hct	49.2 (32.3-65.0)	51.4 (28.0-70.0)*
2 months		
Hb	10.2 (8.3-12.8)	10.1 (8.2-12.6)
Hct	31.3 (22.0-39.1)	31.1 (24.0-40.0)

* $p < 0.05$

Similarly, there was a slightly lower mean hematocrit and hemoglobin at birth among the children in the AZT arm. But, again, this was not clinically significant at all, and by 2 months of age this had resolved without any treatment.



In summary, there were no differences that we detected in terms of signs or symptoms of toxicity, intolerance, or adverse events. The ANC and delivery doses were tolerated well. No woman had to stop treatment because of toxicity or adverse events, and we did not find that adverse events were associated with treatment. We did have high adherence and follow-up throughout in terms of the completeness and reliability of these data.



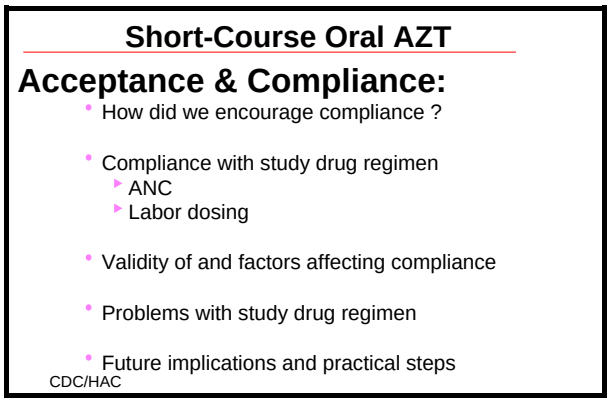
In terms of the implications for the open AZT program, we now recommend in Thailand, based on these results, that there is not a need for special monitoring beyond routine clinical monitoring either for mothers or infants who receive the open AZT. We also do not think that there are any specific criteria for excluding women from a short-course AZT regimen.

We would expect that this should be similar in other developing countries. However, we would hesitate to make a specific recommendation in situations where there are other baseline conditions and other diseases and co-infections. Other local data probably would be needed to better define local monitoring needs.

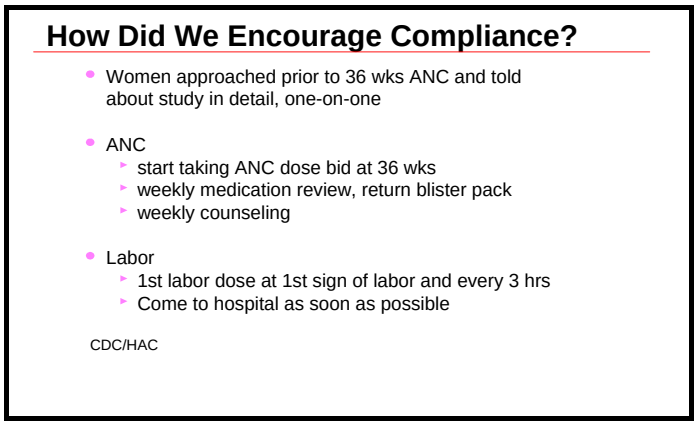
Acceptance and Compliance with the 'Bangkok Regimen'

Thananda Naiwatanakul, M.S.
HIV/AIDS Collaboration, Bangkok, Thailand

I also would like to thank the CDC organizers for the opportunity to attend this workshop and to present some of our work. My presentation is about acceptance and compliance with the "Bangkok Regimen." I will show you that acceptance and adherence, or compliance, were very good. I will show you some of the data and some of the reasons why we think it was so good.



The main topics I will address are: how did we encourage compliance; what data do we have on compliance with the study drug regimen, both the antenatal part and the labor dosing; and how did we assess the validity of the high compliance rate? I also will discuss some of the problems and concerns that we did find, and then discuss future implications and practical steps.



How did we encourage compliance? First, as I think you already know, our study team approached HIV-positive women in ANC well before 36 weeks gestation to begin to tell them about the study and to find out if they would be interested. Eligible women had several private one-on-one sessions to learn about the study and the drug regimen. At 36 weeks, eligible women were enrolled, randomized, and started on study drug. The first pill was taken at the ANC, under observation of a study nurse, and instructions for taking the pills twice a day until labor were reviewed in detail. The women were given blister packs for a week, until their next appointment. To promote compliance, at each weekly ANC visit after 36 weeks, the woman met individually with a study nurse who reviewed the pill-taking for the week, filled out a drug calendar, and checked the used blister packs. The patient was encouraged to discuss any problems concerning pill-taking with the study nurses and counselors.

Women were told that at the first sign of labor they should take one study pill and then come to the hospital as early as possible to begin taking the labor dose every 3 hours in the hospital–this was reenforced at each visit. A packet of labor doses was ready for her at the hospital–when she arrived, she was quickly checked in by the labor room nurse, and a drug form and alarm clock were set at the bedside, so both the woman and the nurse could keep track of when the next labor dose was due.

Short Course AZT Phase III Trial

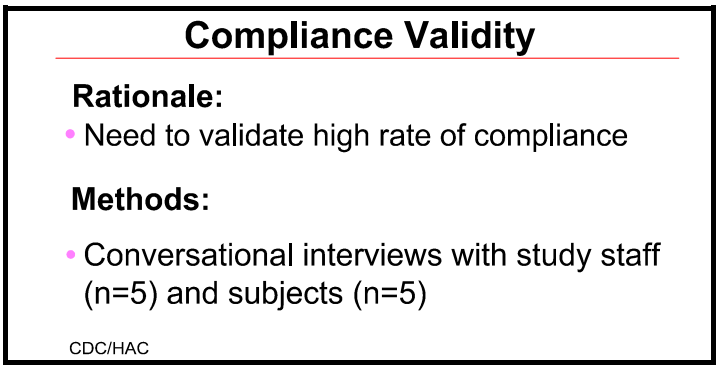
Antenatal Study Drug Compliance

	(n=393*)
Full compliance	99%
Partial noncompliance	1%
Substantial noncompliance	0%

* Study women who have delivered; excludes 4 women who dropped out before delivery

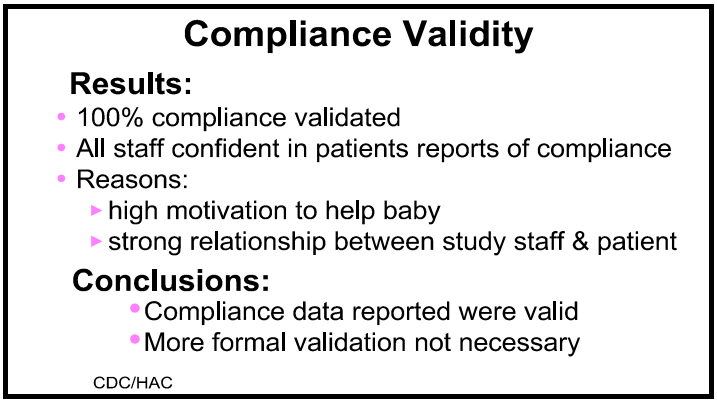
CDC/HAC

We assessed ANC compliance by looking at number of pills missed and 24-hour periods (two consecutive doses missed) without a study pill. As you can see, the rate of compliance was extremely high. Ninety-nine percent of the women met our definition for full compliance, which we defined as not missing more than two study pills in any week and not having any 24-hour period without study drug. Partial noncompliance was defined as missing three to five study pills in 1 week or one to two 24-hour periods without study drug.



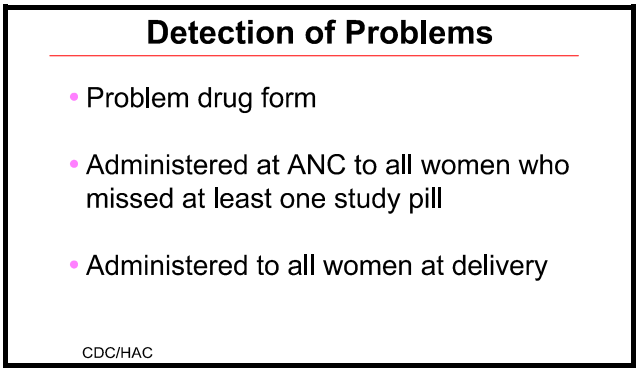
Early in the study when we noted such a high compliance rate, we decided that we should try to validate these data. We thought if there was any suggestion that the compliance rates were not as they seemed that we might need to do a more in-depth study or introduce other measures.

To validate the qualitative pill counts and reports from the women, social scientists on our team conducted open-ended conversational interviews with both study staff and study subjects.



We found that the staff were confident of the high levels of compliance reported–they felt that the study patients would tell them if there were problems. The patients who were interviewed also reported that there were no problems with the drug-taking. Reasons for high compliance included the women's very strong motivation to help their babies and a strong relationship between study staff and patients.

We concluded from this that the antenatal compliance data were valid and that there were compelling factors underlying this high rate of compliance. We decided that a more formal compliance validation study or other interventions were not necessary.



We also monitored compliance by actively looking for problems. To do this, we used a "problem drug form," which we developed before the trial began. The problem drug form was administered to any woman during ANC who reported missing ***any*** study pill. It was also administered ***to all women*** in the study at delivery.

Most Common Reasons for Missing Antenatal Study Pill (N=54)

	n	%
Think you have the placebo	35	*57*
Didn't have pills when needed	33	*54*
Taking pills reminded you of HIV	17	*28*
Too many pills to take	15	*25*
Afraid pills harmful to your baby	15	*25*
Didn't think pills would help	13	*21*
Too busy with work	12	*20*
Hard time remembering to take	10	*16*
Pills made you feel sick	6	*10*

CDC/HAC

There were 54 women who missed at least one study pill during ANC, but most of these women still met our definition for "full compliance." The percentages here are based on the 54 women. Only four women missed two consecutive pills. Women reported not having the pills with them when they needed them, problems taking too many pills, being too busy with work, or having a hard time remembering. Very few complained that the pills made them feel sick. While these problems did not actually interfere with our compliance, they should be considered in open AZT programs.

Women also indicated some concerns that were related to the trial, such as a concern that they had placebo or did not think the pills would help.

Labor Dose Compliance

Home dose	**276/392**	**68%**
Labor dose (at least 1)	**390/392**	**99.5%**
Women with correct number of doses	**350/392**	**89%**

Compliance with the labor dose also was quite good. About 70 percent of the women took a dose at home at the start of labor. Most of the women who did not take a dose at home came to the hospital for a labor check, because they were not sure of the start of labor or they already were in the hospital at the start of labor. Only two women had no labor dose at all. In this regimen, women were supposed to have one drug dose every 3 hours during labor. By comparing the number of labor hours with the number of labor doses women received, we estimated that about 90 percent of the women received their complete labor dose.

Problems with Taking Study Drug During Labor

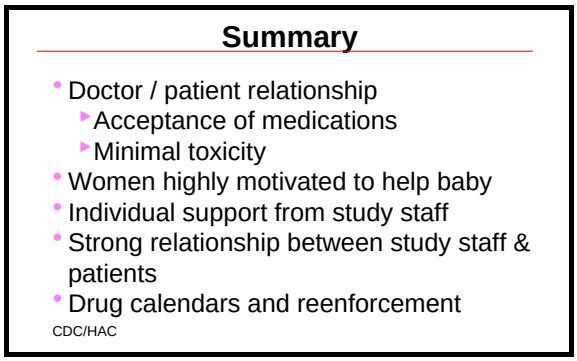
	n	%
No problem	269	68
Any problem	126	32
Nausea	2	0.5
Vomiting	9	2
Other (e.g. insure of true labor)	115	29

Any problems with taking the study drug during labor were recorded by the hospital nursing staff and reviewed by the study staff. As you can see, delivery dosing problems were reported for 32 percent of women. However, when we look at what types of problems these were, very few were physical problems that interfered with the labor dose. Most of the problems with labor dose were due to some misunderstanding or logistical problems–such as not being sure whether the woman actually was in labor and should start the pills every 3 hours, false labor, or not recognizing immediately that the woman was in the study.

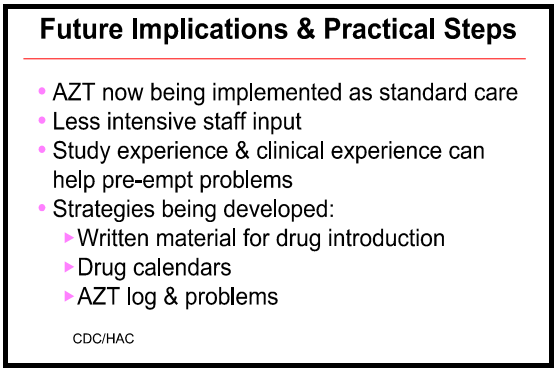
Reasons Drug Taking Was Stopped or Delayed During Labor

	n
Not sure of true labor	20
Staff mistake/forgot	8
Patient mistake/forgot	3
C-section preparation	1
Total	36

Problems that resulted in the delivery dose being stopped or delayed beyond the accepted interval were reported for only 36 women. Similarly, these all were due to misunderstanding or logistical problems. It is important to emphasize that no woman had to stop the labor dosing because of a bad reaction or problem.



In summary, we are very confident that there was a very high level of compliance in our study. We think this was due to several factors. In Thailand, patients have strong respect for medical advice given by doctors and nurses–we were not surprised that they would accept medications recommended by the medical staff, especially when toxicity was minimal. The pregnant women also were highly motivated to help their babies–taking the medication was a positive action of hope. We also had a very strong relationship between study subjects and study staff, which was reenforced by external reminders such as the drug calendar and the weekly individual medication reviews.



As we all know, an intensive clinical trial is very different from a mass treatment program. In most settings where short-course AZT will be implemented, the intensive input from study staff that was part of the Bangkok trial will not be possible–therefore, compliance may not be as good. However, based on our experience, we can develop strategies to promote compliance and avoid problems. We now are beginning to implement short-course AZT as standard care in the two hospitals where we conducted the trial. Some strategies we

are developing to improve compliance include provision of written materials for women upon introduction to the program to reenforce shorter verbal instructions and drug calendars that women can use to help remind themselves of when they are supposed to be taking the drug. We also are maintaining antenatal and delivery room logs to monitor problems associated with taking AZT.